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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/783,391	02/20/2004	Pedro Aza-Blanc	P1111US10	6423

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EXAMINER	
BRISTOL, LYNN ANNE	
ART UNIT	PAPER NUMBER
1643	

NOTIFICATION DATE	DELIVERY MODE
07/07/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

IPLegal@gnf.org
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Office Action Summary	Application No.	Applicant(s)	
	10/783,391	AZA-BLANC ET AL.	
	Examiner	Art Unit	
	LYNN BRISTOL	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 April 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *27-33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *27-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 27-33 are all the pending claims for this application.

2. Claims 27-33 were amended in the Response of 4/10/08.

3. This action is FINAL.

Withdrawal of Objections

Specification

4. The amendment to the specification filed in the Response of 8/2/07 has now been considered and entered because Applicants have only now provided instructions in the Response of 4/10/08.

Rejections Maintained

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement

5. The rejection of Claims 27-33 under 35 U.S.C. 112, first paragraph, in lacking enablement for identifying any test agent used in the screening method based on modulation of JIK kinase activity and modulation of TRAIL-induced apoptosis vis-à-vis the measurement of any apoptosis activity in any cell or cell line under just any conditions much less in the absence of specific controls, or in using the method in a subject is maintained.

For purposes of review, the rejection was set forth in the Office Action of 10/18/07 as follows:

"The assay for apoptosis activity in step d) is not limited to an activity exclusively associated with TRAIL, the apoptosis activity may be mediated by any other molecule in a signaling pathway for apoptosis in the cell system. The claims are not limited to any controls, which would distinguish TRAIL-dependent from the TRAIL-independent apoptosis activity. The claims are not limited to the TRAIL-dependent caspase activation being quantitatively different than TRAIL-independent caspase activity.

Disclosure in the Specification

Examples 1 and 2 of the specification and Aza-Blanc et al. (Molecular Cell 12:627-637 (2003); post-filing date publication by the instant inventors) teach a very specific method for identifying genes that effect (enhance/inhibit) TRAIL-induced apoptosis by screening HeLa cells using a siRNA directed against 510 genes including most kinases, i.e., JIK. To identify agents, the effects of the siRNA transfection on cell viability in the presence and absence of TRAIL was compared. For example, JIK-specific siRNA and *relevant controls* were transfected into HeLa cells in duplicate, and TRAIL was added to one cell group for an additional 24 hr period followed by cell viability measurement. The effect of siRNA on TRAIL-dependent death was calculated as the ratio of viability in the presence versus the absence of TRAIL. Transfection of JIK-specific siRNA into HeLa cells enhanced cell death in a TRAIL-dependent manner. Also, HeLa cells treated with JIK-specific siRNA showed TRAIL-dependent and –independent caspase activity, indicating that JIK has a more general anti-apoptotic role and that removing the biological activity (deleting the gene product) sensitizes cells to TRAIL-induced death.

Additionally, Applicant's specification and Aza-Blanc et al. (p. 631, Col. 1, ¶3) both caution that "one potential concern in using siRNAs for phenotypic screens is that since siRNAs are not 100% selective for the intended mRNA target the observed phenotype could be due to inhibition of either the intended target or an off-target mRNA." It is apparent that in practicing the claimed method invention, one of skill in the art would need to be apprised of the non-specificity for some iRNAs in the targeting method and that performing numerous specific controls would be required to practice the method steps.

The specification does not demonstrate that any other agent than a JIK-specific RNAi was identified by the instant claimed method. The specification is not enabling for a method that would allow one of ordinary skill in the art to identify any test agent that meets all the limitations of the instant claims much less which could be practiced in a subject.

Thus, without there being a reasonable number of test agents having been identified by the claimed method, the use of the screening method for identifying a specific and substantial test agent is unpredictable and the experimentation left to those skilled in the art is unnecessarily and improperly extensive and undue. See Amgen, Inc. v. Chugai Pharmaceutical Co. Ltd., 927 F.2d 1200, 18 USPQ 1016 (Fed. Cir. 1991) at 18 USPQ 1026 1027 and Ex parte Forman, 230 USPQ 546 (BPAI 1986).

One of skill in the art could not practice the method with a reasonable expectation of success, absent examples providing evidence, which is reasonably predictive for the breadth of the claimed method steps in any cell or cell type, and using just any apoptosis assay in order to correlate the apoptosis activity with TRAIL-induced apoptosis. The enablement provided by the specification is not commensurate in scope with the claimed invention."

Applicants' allegations on pp. 6-7 of the Response of 4/10/08 have been considered but are not found persuasive. Applicants are seemly under the assumption that by amending Claim 27 to include a control cell system, the second cell system that is the same as the first cell system, that the claims are enabled for screening any agent and in any cell irrespective of whether the skilled artisan is aware of there being any

pre-existing or inherent association between TRAIL responsiveness and JIK kinase activity for the cell.

Examiner's Reply

The examiner submits that Applicants have yet to identify any other cell-based assay, in vitro or in a subject, where they show a direct correlation between TRAIL-responsiveness and JIK kinase activity within the same cell. Applicants have not shown any relationship between JIK kinase activity, TRAIL responsiveness ***and*** TRAIL-induced apoptosis in any other cell, but for HeLa cells. This is a substantial omission of critical evidence because this precise correlation between these cell signaling molecules is essential in order for the method invention to be operative. Can the assay be performed on any other cells than the HeLa cell line? What other agents have been identified using the HeLa cell line. What other agents have been identified using any other cell-based assay? Applicants have not identified how the screening assay could be performed "in a subject" (Claim 32, for example) and how the biological materials are then assayed for apoptosis activity.

Claims 27-33 are amended to recite the "first cell system" and "second cell system" in Claim 27. The meaning of a "cell system" is not clear from the claims or the specification and there is no art recognized definition for the phrase. Does this refer to a functional intact cell or a cell lysate comprising functional enzymes for JIK kinase? The specification defines "a typical cell based assay for screening test agents for modulators of expression of an apoptosis-modulatory polypeptide, a construct comprising a transcription regulatory element of the apoptosis-modulatory polypeptide that is

operably linked to a reporter gene is introduced into a *host cell system*. The reporter gene activity (e.g., an enzymatic activity) in the presence of a test agent can be determined and compared to the activity of the reporter gene in the absence of the test agent" [45]. Thus, the specification does not clearly define a first and second cell system for any kind of cell, only the example of the "host cell system" as above. The specification does not support performing a method requiring a recombinant host cell system in any subject.

Applicants' amendments to the claims have raised more issues than resolved any of the outstanding enablement issues for these claims.

The specification is enabling for a) screening a test agent in a bioassay measuring JIK kinase activity and in a bioassay measuring TRAIL-induced apoptosis using an RNAi-based loss of function screening method for identification of test agents/modulators of TRAIL-induced apoptosis in HeLa cells and b) identifying the JIK gene vis-à-vis the RNAi screening method with a JIK-specific RNAi test agent in HeLa cells. However, the claim scope far exceeds what the ordinary artisan is enabled to practice based on the written description alone in the specification. The rejection is maintained.

Conclusion

6. No claims are allowed.

7. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lynn Bristol whose telephone number is 571-272-6883. The examiner can normally be reached on 8:00-4:00, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

LAB

/David J Blanchard/
Primary Examiner, Art Unit 1643